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Serum Carnitine Concentrations and Cardiac Function in Pediatric, Adolescent and Young Adult Oncology Patients Receiving High-Dose Anthracyclines

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OBJECTIVE Anthracycline chemotherapy agents have significant dose-dependent cardiotoxic effects. Carnitine, a non-essential amino acid, is involved in long chain fatty acid oxidation, and carnitine deficiency can result in cardiomyopathy and cardiac arrhythmias. If administered concurrently with chemotherapy, carnitine supplementation could be a potential strategy to prevent cardiotoxicity. However, the association between serum carnitine concentrations and anthracycline cardiotoxicity during cancer treatment in the childhood, adolescent, and young adult (CAYA) age range has not been established.

METHODS This prospective pilot cohort study characterized changes in serum carnitine concentrations and cardiac function before, during, and approximately 1 year after large-dose anthracycline therapy in newly diagnosed CAYA cancer patients.

RESULTS Among 21 patients with a mean cumulative anthracycline dose exposure of 409 mg/m^2 of doxorubicin equivalents, left ventricular ejection fraction and relative wall thickness decreased, indicating an overall decline in cardiac function. A reversible decrease in serum carnitine concentrations was also observed. A non-statistically significant positive correlation was observed; for every 1 mmol/L decrease in serum carnitine concentration, there was a 0.09% decrease in LVEF ($p = 0.2$).

CONCLUSIONS These findings from this small pilot study suggest that there may be a relationship between serum carnitine concentrations and cardiac function after anthracycline therapy that should be evaluated in larger studies.

ABBREVIATIONS AML, acute myeloid leukemia; CAYA, childhood, adolescent and young adult; COG, Children's Oncology Group; CPX-351, dual-drug liposomal cytarabine and daunorubicin; LCFA, long chain fatty acids; LOESS, locally estimated scatterplot smoothing; LV, left ventricle; LVEF, left ventricular ejection fraction; RCHSD, Rady Children's Hospital San Diego; RWT, relative wall thickness.

KEYWORDS anthracyclines; cardiotoxicity; carnitine; pediatric oncology

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Introduction

Improvements in diagnostic precision, therapy, and supportive care have resulted in a growing population of childhood, adolescent and young adult (CAYA) cancer survivors. However, cardiovascular disease is a leading cause of death among survivors.[1] Anthracycline chemotherapy agents, including doxorubicin, daunorubicin, idarubicin, and mitoxantrone, are used to treat a variety of CAYA cancers, including acute myeloid leukemia (AML) and bone tumors, but have significant dose-dependent cardiotoxic effects.[2] The cardiotoxicity that results can vary from asymptomatic functional or structural abnormalities only detected on imaging studies, to clinically significant heart failure. It is estimated that 1 in 10 children treated with large-dose anthracyclines, defined as 250 mg/m^2 of doxorubicin equivalents or greater, will develop heart failure.[2] In the Childhood Cancer Survivor Study, which included patients diagnosed before age 21 years, CAYA patients treated with large-dose anthracyclines, defined as 250 mg/m^2 of doxorubicin equivalents or greater had a significantly higher risk of developing heart failure.[3] Outcome following onset of symptomatic heart failure is poor, as the 5-year survival rate is less than 50%, emphasizing the need for early screening and prevention of symptomatic cardiac dysfunction.[4]

Anthracyclines exert their effect on cancer cells by intercalating between DNA base pairs and inhibiting the activity of multiple enzymes required for DNA replication, effectively inhibiting cancer cell proliferation.

Via the generation of free radicals and reactive oxygen species, disruption of myocyte fatty acid oxidation, disruption of the electron transport chain, and formation of iron complexes, anthracyclines may also cause cardiac myocyte injury.[5] It is thought that since cardiac myocytes have low levels of free radical scavenger proteins, they are at increased susceptibility to damage.[5–7] If enough myocardial damage occurs, the chamber walls become thinner and the heart increases in size, similar to the changes that are seen in dilated cardiomyopathy.[8] It is not completely understood how anthracyclines induce their cardiotoxic effects at the cellular level, but a better understanding of the mechanisms involved would allow for better primary and secondary prevention strategies.

A previous study looked at the metabolomic profile of 150 survivors of childhood cancer and found that 15 compounds in the carbohydrate, amino acid and lipid metabolism pathways were significantly different between patients with and without cardiac dysfunction.[9] After adjusting for multiple comparisons, it was found that patients with cardiac dysfunction had significantly lower serum carnitine concentrations and higher levels of essential and long chain fatty acids (LCFA). Carnitine is a non-essential amino acid, and in humans most of the carnitine in our body is obtained from food sources, while the remainder is formed endogenously in the kidney, liver, and brain. Cardiac myocytes contain relatively high concentrations of carnitine, which is essential for oxidation of LCFAs, which are a major substrate for energy production in the myocardium.[9,10] Carnitine is actively transported into the cell since myocytes are incapable of carnitine biosynthesis. Clinically, both primary and secondary carnitine deficiency can result in cardiomyopathy and cardiac arrhythmias, due in part to the accumulation of LCFAs and acylcarnitines that are unable to be oxidized in the mitochondria and are unavailable for energy production.[11,12]

If administered concurrently with chemotherapy, carnitine supplementation could be a potential strategy to prevent cardiotoxicity. However, the association between serum carnitine concentrations and anthracycline cardiotoxicity during cancer treatment has not been established. Our objective was to characterize changes in serum carnitine concentrations and cardiac function with large-dose anthracycline therapy in children. In this small prospective pilot cohort study, we described changes in serum carnitine concentrations and cardiac function, measured through left ventricular ejection fraction (LVEF) and relative wall thickness (RWT), in CAYA patients with a new diagnosis of cancer before, during, and after large-dose anthracycline therapy.

Methods

Patient Selection. CAYA patients at Rady Children's Hospital San Diego (RCHSD) between 1 to 25 years of age with a new diagnosis of cancer who had a proposed treatment plan that included a cumulative anthracycline dose greater than 250 mg/m^2 of cumulative doxorubicin equivalents, between September 1, 2018, to March 2, 2023, were eligible to participate in this prospective, pilot cohort study. Patients were excluded if they had a previous diagnosis of reduced ventricular cardiac dysfunction, defined as: shortening fraction of less than 28% or LVEF of less than 50% by echocardiogram.

Data Collection. Study participants had total serum carnitine concentrations measured at the following 5 time points: the time of diagnosis prior to the administration of any cardiotoxic chemotherapy, after the first cycle of anthracycline therapy, prior to the start of the second cycle of anthracycline therapy, at the end of therapy, and approximately 12 months after completion of treatment. Patients also underwent echocardiography screening per our institution's standard of care for their respective chemotherapy protocols. LVEF by the 5/6 area–length method and RWT, calculated as septal wall thickness plus posterior wall thickness divided by LV diastolic diameter, were extracted from echocardiogram reports.[13,14] The 4 time points for the echocardiographic measurements for this study were intended to correlate roughly with the time points at which serum carnitine concentrations were collected and included: the time of diagnosis, after at least 1 cycle of anthracycline therapy, at the end of therapy, and approximately 12 months after completion of treatment. Due to an inability to ensure timely follow-up related to patients' clinical schedules and preferences, and research restrictions and other factors during the COVID-19 pandemic, the final timepoints for both carnitine measurement and echocardiography was extended to the next available assessment, up to a maximum of 3 years post-therapy. Doxorubicin equivalents of anthracycline doses were calculated based on the Children's Oncology Group (COG) long-term follow-up guidelines for daunorubicin and idarubicin, as well as published data by Feijen et al[15] for mitoxantrone.[16] Other data points collected included administration of dexrazoxane or other medications that may affect cardiac remodeling, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers.

Statistical Methods. Descriptive statistics concentrated on the trends of the serum carnitine concentrations over multiple anthracycline treatments, and the associations between serum carnitine concentration, potential confounders, and cardiotoxicity measures. Locally estimated scatterplot smoothing (LOESS) curves were used to illustrate serum carnitine concentrations and cardiac function over time. Pearson correlation measurements were also used to evaluate the associations between changes in serum carnitine concentrations and LVEF. Given the exploratory nature of the study and the likelihood that there would

be participant loss to follow-up due to patient attrition or death, all collected data for patients was included in the analysis. This would increase the width of the confidence intervals for data analysis as follow-up time progressed due to smaller sample sizes at later timepoints but would not have an impact on our conclusions as our findings were intended to provide a preliminary effect size and descriptive data, which may be used to design future studies with greater statistical power.

Results

Patient Characteristics. Twenty-one patients participated in the study. Patient demographics are displayed in the Table. The median age at time of cancer diagnosis was 13 years, with the most common diagnoses being osteosarcoma, AML, and Ewing sarcoma. Two patients had a history of cardiac abnormalities at baseline. One of these patients had trisomy 21 and a patent ductus arteriosus status post device closure. The second patient had left ventricular dilation and low normal LVEF of 56%. Four patients (19%) died during the study period. These deaths and other factors mainly related to the COVID-19 pandemic led to 21 missing serum carnitine data points out of 105 possible carnitine collections, with the vast majority (15) being with the last (fifth) time point.

Therapies Received. The mean cumulative anthracycline exposure was 409 mg/m^2 of doxorubicin equivalents with a median of 446 mg/m^2, a 25th percentile of 369 mg/m^2, and a 75th percentile of 451 mg/m^2. The mean duration of therapy (time between diagnosis and end of therapy) was 297 days with a median of 246 days, 25th percentile of 202 days, and a 75th percentile of 307 days. While the participants were chosen because of expectations of receiving high cumulative anthracycline doses, 2 of the 21 ultimately received less than 250 mg/m^2 due to their individual treatment considerations. Patients with AML were treated with a variety of regimens, including combinations of daunorubicin, idarubicin, mitoxantrone, and dual-drug liposomal cytarabine and daunorubicin (CPX-351). Doxorubicin was used to treat patients with all the other cancer diagnoses in this study. All patients received dexrazoxane as a cardioprotective agent concurrently with their anthracycline chemotherapy, except with CPX-351, which only 1 patient received. One patient received direct chest radiation. In addition, 1 patient was started on an angiotensin-converting enzyme inhibitor for hypertension during the study period.

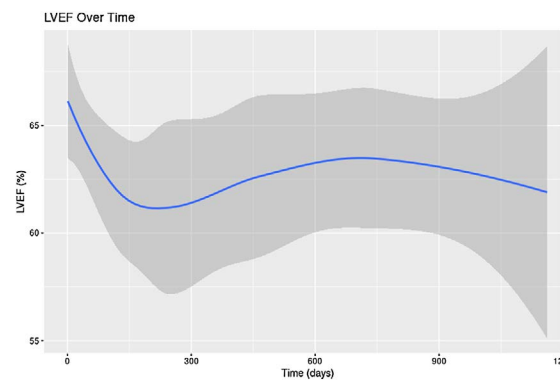
Cardiac Function. Fifteen participants had 4 echocardiograms' data collected during the study period. Five participants had 3 echocardiograms' data collected during the study period. One participant had 2 echocardiograms' data collected during the study period. The x-axes of Figures 1 and 2 represent the time in days after the first echocardiogram obtained during the study observation period. Regarding the number of days between the first echocardiogram and the last echocardiogram, the average time was 604 days with a range of 43 to 1161 days, and the median was 590 days, 25th percentile was 380 days, and 75th percentile was 743 days.

As anthracycline exposure increased for each patient over time on treatment, a decline in LVEF was observed, eventually stabilizing at a value lower than the baseline value (Figure 1). Prior to therapy, the mean LVEF was 64.9%, but decreased to 62.2% one year after therapy completion. Thirteen patients (62%) had a 5% decrease

Table. Baseline Patient Demographics

	Total (N = 21)
Age at diagnosis, median [min, max]	13 [1, 19]
Sex, N (%)	
Female	9 (43)
Male	12 (57)
Diagnosis, N (%)	
Acute myeloid leukemia (AML)	5 (24)
Ewing sarcoma	4 (19)
Malignant rhabdoid tumor of the kidney	1 (5)
Myelodysplastic syndrome (MDS)	1 (5)
Osteosarcoma	9 (43)
Undifferentiated sarcoma	1 (5)
Race, N (%)	
Black	2 (10)
Hispanic	7 (33)
White	11 (52)
Other	1 (5)

Figure 1. LOESS curve of LVEF over time, beginning on the day of baseline echocardiogram prior to anthracycline therapy, and continuing through therapy and until at least 1 year after therapy.



LOESS, locally estimated scatterplot smoothing; LVEF, left ventricular ejection fraction.

in LVEF from baseline at some point during the study period. The mean RWT at baseline was 0.33 and increased initially during anthracycline therapy. However, by the end of therapy, RWT decreased and had a mean of 0.3 one year after therapy ended (Figure 2).

Serum Carnitine Concentrations. Six participants had 5 carnitine concentrations drawn. Nine participants had 4 carnitine concentrations drawn. Six participants had 3 carnitine concentrations drawn. The x-axis of Figure 3 represents the time in days after the first echocardiogram obtained during the study observation period. Regarding the number of days between the first echocardiogram and the last serum carnitine collection, the average time was 307 days with a range of 26 to 793, and the median was 244 days, 25th percentile was 141 days, and 75th percentile was 463 days.

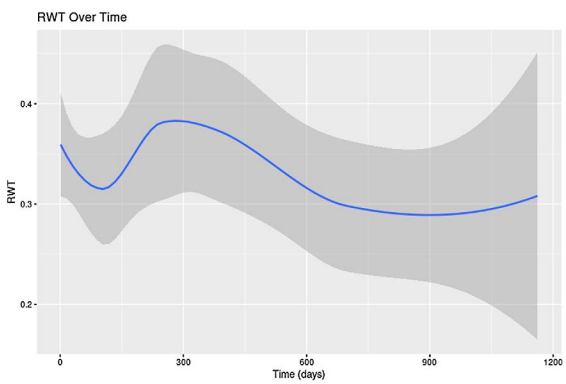
The trend of total serum carnitine concentrations over time is depicted in Figure 3. During anthracycline therapy, patients' serum carnitine concentrations declined. The baseline average total serum carnitine concentrations were 37.6 mmol/L (range, 14.7–65.6 mmol/L). The lowest total serum carnitine concentration on average was 30.5 mmol/L (range, 14.7–51.4 mmol/L). However, 1 year after completion of therapy, total serum carnitine concentrations increased back to baseline values. When the association between serum carnitine concentrations and LVEF was analyzed, a non-statistically significant positive correlation was observed, and for every 1 mmol/L decrease in serum carnitine concentration, there was a 0.09% decrease in LVEF ($r(19) = 0.2$, $p = 0.2$).

Discussion

Understanding and preventing treatment-related cardiotoxicity is extremely important for maintaining the long-term health of CAYA cancer survivors, especially because cardiotoxicity can often be initially subclinical and difficult to detect with severe, long-term outcomes. Currently the only prophylactic agent utilized to prevent cardiac dysfunction in patients receiving large-dose anthracycline chemotherapy is dexrazoxane administered prior to chemotherapy.[17] Liposomal formulations of anthracyclines have also been designed to minimize cardiotoxic effects, and are currently being studied in CAYA AML.[18] Our study suggests a possible relationship between serum carnitine concentrations and cardiac dysfunction after large-dose anthracycline exposure, and that further research is warranted to evaluate carnitine as a novel prophylactic agent to mitigate anthracycline-induced cardiotoxicity.

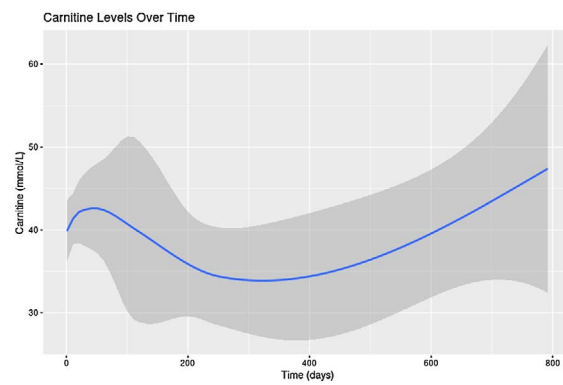
We report that in CAYA patients receiving large-dose anthracyclines, LVEF initially decreased then stabilized at a lower baseline following completion of therapy, consistent with previous literature.[19] An overall decrease in RWT was also observed following therapy, which may be representative of the long-term thinning of the ventricular walls seen in cardiomyopathy. Patients had a temporary increase in RWT within the first year of therapy initiation, which could be related to the initial increase in LV mass that has previously been reported in some studies after anthracycline therapy in both adults and children and may represent transient edema.[20–22] However, this finding has not been consistent across the literature.[23,24] Additionally, we report that a reversible decline in total serum carnitine concentrations was observed throughout the time that patients received anthracyclines. At the timepoint 1 year after completing chemotherapy, the patient's serum carnitine concentrations had returned to their pre-treatment baselines. A positive correlation between decreased

Figure 2. LOESS curves of RWT over time, beginning on the day of baseline echocardiogram prior to anthracycline therapy, and continuing throughout therapy and until at least 1 year after therapy.



LOESS, locally estimated scatterplot smoothing; RWT, relative wall thickness.

Figure 3. LOESS curves of serum carnitine concentrations over time, beginning on the day of baseline echocardiogram prior to anthracycline therapy, and continuing throughout therapy and until at least 1 year after therapy.



LOESS, locally estimated scatterplot smoothing.

carnitine concentrations and LVEF was found, but was not of statistical significance, as expected given that this study of 21 patients was not powered to detect such an association. Based on the power analysis for a significance level of 0.05 and a power level of 0.8, the sample size needed to detect such an effect would be 193 subjects. To calculate that estimated sample size, the "pwr.r.test" function in RStudio was used (https://cran.r-project.org/web/packages/pwr/pwr.pdf).

Although the protective role of carnitine against cardiac dysfunction is unclear, we offer several hypotheses about the observed trends in serum carnitine concentrations. Anthracyclines may exert at least part of their cardiotoxicity by inhibiting LCFA oxidation in the heart, as previous studies also suggested.[25] In addition, although some carnitine is formed endogenously, the primary source of carnitine for humans is dietary, especially animal products.[10,26] Dietary intake among oncology patients is often poor during treatment with chemotherapy, radiotherapy, surgery and hematopoietic stem cell transplant, due to factors such as therapy-induced nausea and vomiting, mucositis, pain, fatigue, changes in taste, loss of appetite, diarrhea, and constipation.[27] Furthermore, in additional to decreased dietary intake, secondary carnitine deficiency can be due to increased renal losses of carnitine, which can be caused by kidney-damaging chemotherapy.[28] As these acute adverse effects of anti-cancer therapy subside, nutrition, renal function and serum carnitine levels would be expected improve in most patients. These observations reveal an opportunity to provide nutritional support with exogenous carnitine at times of decreased dietary intake and increased renal loss.

The findings of this study provide a basis for further studies to determine the role of carnitine in anthracycline-related cardiotoxicity and whether carnitine supplementation may mitigate the cardiac dysfunction related to anthracycline therapy. Levocarnitine is a nutritional supplement that is inexpensive, readily available, can be administered orally, and has a low side effect profile.[29] The use of levocarnitine prophylaxis to prevent asparaginase-associated hepatotoxicity in adolescents and young adults with acute lymphoblastic leukemia is currently being studied by COG (NCT05602194). Further research is needed to evaluate definitively the association between serum carnitine concentrations and cardiac function after anthracycline therapy and may provide justification for a similar strategy to prevent anthracycline cardiotoxicity.

There were several limitations to this study. First, since the primary aim of this study was to generate hypotheses for future larger studies, only limited analyses were performed. Second, only a small number of patients from a single center were enrolled and some patients passed away during the study data collection period, limiting the statistical power and potentially the generalizability of the findings. Third, in the interest of having a broader catchment, there were not extensive exclusion criteria beyond the entry criteria of having an adequate ejection fraction or shortening fraction. As a result, other potential confounders such as hypertension or static anatomic echocardiographic measurements such as ventricular volume were not included in the exclusion criteria. Nonetheless, as each patient was followed longitudinally and there were not expected to be interactions between carnitine and these potential confounders, the data of these patients remains valuable for and included in the analysis. Fourth, as anthracycline exposure is the main risk factor for heart damage in chemotherapy, the study was not designed to evaluate other causes of heart damage, such as sepsis, pericarditis, or myocardial infarction. As this study was designed as an intention to treat study, without a plan to remove participants who did not reach the expected anthracycline exposure due to individual clinical considerations, the serum carnitine and echocardiogram data of the 2 patients who did not meet the expected 250 mg/m^2 of doxorubicin equivalents were included in the analysis. Fifth, echocardiograms beyond standard of care screening were not conducted for the purpose of this study, so the dates that echocardiograms were performed did not always match the same dates that serum carnitine concentrations were obtained. However, as the study reported the echocardiogram and carnitine concentrations in the figures with time as a continuous variable, the variability in the exact time points is accounted for in the data presented in the LOESS graphs.

In conclusion, this prospective pilot cohort study builds upon previous findings that serum carnitine concentrations may be low in patients at risk for cardiotoxicity due to large-dose anthracycline therapy and further investigates the relationship between serum carnitine and cardiotoxicity in the CAYA oncology patients. We observed a reversible decline in serum carnitine concentrations and a general decline in heart function during the study period, in addition to a non-statistically significant association between serum carnitine concentrations and cardiac function. Our early findings suggest the potential benefits for a more definitive evaluation of the potential relationship between carnitine levels and cardiac function after anthracycline therapy in larger studies.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the institutional review board at the University of California, San Diego. All patients and/or parents/caregiver(s) provided written informed consent and/or assent (as applicable) at enrollment.

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